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# NF1

1996

1997

## Molecular Biology & Genetics

Genetic nature of NF1 documented by Thomson (1900), Adrian (1901), and Prieser & Davenport (1918)

NF1 gene localized to chromosome 17 1987

LOH on chromosome 17 shown for MPNSTs 1989

• NF1 gene cloned 1990  
• NF1 classified as a tumor suppressor 1990

Neurofibromin identified as the product of the NF1 gene 1991

Splice variants of NF1 identified 1992

• NF2 gene cloned 1993  
• NF2 gene product identified as Merlin/Schwannomin 1993

NF1 mRNA shows high levels of editing – potential mechanism for inactivation without mutation 1995

Evidence for LOH of NF1 in neurofibromas 1995

Identification of a point mutation in a dermal neurofibroma – supports the tumor suppressor hypothesis 1996

## Cellular Biology

NF1 shares homology with GAP proteins 1990

Development of intracellular Ras-GTP to Ras-GDP ratio for measuring neurofibromin-specific GAP activity 1992

Neurofibromin interacts with microtubules 1993

Ras-GTP to Ras-GDP ratio elevated in neurofibromas and MPNSTs 1996

• NF1<sup>-/-</sup> Schwann cells proliferate in response to forskolin; NF1<sup>+/+</sup> and NF1<sup>+/+</sup> Schwann cells do not 1997  
• NF1<sup>-/-</sup> Schwann cells have a growth advantage and are easily transformed 1997

Neurofibromin regulates protein kinase A 1997

## Pathobiology

1<sup>st</sup> recorded case of optic pathway glioma in association with NF1 1873

Schwann cells from neurofibromas promote angiogenesis and invasion 1990

Loss of NF1 associated with MPNSTs 1992

NF1-related vasculopathy caused by smooth muscle cell proliferation 1993

p53 regulation is involved in the development of MPNSTs 1994

Loss of NF1 associated with the development of leukemias and MPNSTs 1996

Microdeletion of NF1 and surrounding genes associated with facial anomalies and early onset 1997

NF1<sup>-/-</sup> and NF1<sup>+/+</sup> Schwann cells are both angiogenic and invasive in culture 1997

## Technology/ Animal Models

NF1<sup>-/-</sup> mice die of cardiac muscle malformation at gestational day 14 1994

NF1<sup>-/-</sup> mice developed that are tumor prone and develop myeloid leukemias and pheochromocytomas 1994

Improved mouse model of myeloid leukemia developed 1996

Mouse model of learning and memory defects developed 1997

Drosophila model of NF1 developed 1997

## Behavioral & Cognitive Biology

Children with NF1 shown to have high index of specific learning disabilities 1981

Evidence for lower IQ scores in some children with NF1 1986

MRI “abnormalities” associated with learning disabilities in NF1 1994

Pathology of NF1 correlated to MRI data – myelin edema associated with glial proliferation 1995

1<sup>st</sup> research addressing the molecular basis of learning disabilities in NF1 1996

Drosophila NF1 involved in growth, learning, and memory 1997

Cognitive defects detected in NF1<sup>-/-</sup> mice 1997

## Imaging, Detection & Diagnosis

1<sup>st</sup> identified in the literature by Dr. Friedrich von Recklinghausen 1882

1<sup>st</sup> diagnostic test criteria developed for NF 1988

1<sup>st</sup> comprehensive international database for NF developed 1989

Direct gene testing for NF1 available 1995

## Epidemiology

## Experimental Therapeutics

1<sup>st</sup> national multicenter clinical trial for NF began 1994

Translational Research: compound testing for NF1 treatments began 1997

## Symptom Management

Neurofibromas removed surgically

CO<sub>2</sub> laser treatment used for cutaneous neurofibromas 1987

Assessment of surgical removal of plexiform neurofibromas – 86% of tumors did not progress and 20% of cases found improvement 1997

## Important Meetings & Symposia

Foundation of NNFF 1978

NIH Consensus Development Conference on Neurofibromatosis: delineated NF1 from NF2 and diagnostic criteria for each 1987

Foundation of NF, Inc. 1988

DoD Neurofibromatosis Research Program (NFRP) established 1996

NNFF Clinical Care Advisory Board: Diagnostic Evaluation and Management of NF1 and NF2 1997

# Neurofibromatosis Type 1 (NF1)

1998

1999

2000

2001

Structure of the catalytic domain of *NF1* determined  
1998

Homologous, REP-mediated recombination between chromosomes proposed as cause of LOH in patients with deletions  
2000/2001

*Epi1* identified as "second hit" involved in AML development and progression  
2001

Schwann cells proposed as source of LOH and tumor formation in NF1  
2000

NF1<sup>+/-</sup> mast cells show increased proliferation and hyperactivation of Ras  
2000

Sera from NF1 patients shows increased mitogenic activity on Schwann cells in culture  
1998

p53 immunoreactivity is higher in MPNSTs than in benign neurofibromas  
1998

*INK4A* is frequently mutated in MPNSTs, but not neurofibromas  
1999

NF1<sup>+/-</sup> mice develop astrocytomas  
1999

Loss of *NF1* associated with astrocytomas and neurofibromas  
2000

Nerve grafting/wounding causes hyperpigmentation in NF1<sup>+/-</sup> mice  
2000

NF1<sup>+/-</sup>:p53<sup>+/-</sup> tumors overexpress EGFR – possible therapeutic target  
2001

NF1<sup>+/-</sup> chimeric mouse developed – mice develop multiple neurofibromas that are NF1<sup>+/-</sup>  
1999

NF1<sup>+/-</sup>:p53<sup>+/-</sup> mouse developed – model of MPNST development as well as astrocytomas and glioblastomas  
1999

NF1 regulates the learning pathway in *Drosophila*  
2000

NF1<sup>23b/+</sup> mouse developed that lacks only NF1 splice variant type II – not susceptible to tumors but has learning disabilities  
2001

Conditional NF1<sup>+/-</sup> mouse developed that allows targeting of specific cells  
2001

Epidemiologic study of 4402 NF1 patients from three databases identifies specific associations between features  
2000

Farnesyl transferase inhibitors tested for therapeutic effects on NF1  
1999

NINDS Workshop: Defining the Future of Neurofibromatosis Research  
2000

# NF1

Linked research  
Abc NFRP-funded research

2002

2003

2004

2005

Molecular  
Biology &  
Genetics

Cellular  
Biology

Pathobiology

Technology/  
Animal  
Models

Behavioral &  
Cognitive  
Biology

Imaging,  
Detection  
& Diagnosis

Epidemiology

Experimental  
Therapeutics

Symptom  
Management

Important  
Meetings  
& Symposia

Specific ablation of *NF1* in Schwann cells causes the formation of plexiform neurofibromas  
2002

Invasive phenotype of MPNST cells does not involve Ras but is dependent on Src kinase activity and Src-dependent elevation of CD44 expression  
2003

Specific ablation of *NF1* in endothelial cells causes multiple cardiovascular abnormalities that are associated with elevated ras signaling  
2003

*NF1*<sup>+/-</sup> mice lacking *NF1* in astrocytes develop optic nerve gliomas  
2003

Somatic inactivation of *NF1* in hematopoietic cells causes progressive myeloproliferative disease  
2004

Expression of activated TC21/R-Ras2 enhances migration of *NF1*-deficient mouse Schwann cells  
2004

Aberrant activation of the calcium signaling pathway by PDGF B chains contributes to MPNST formation  
2005

EGFR expression in Schwann cells causes nerve hyperplasia with occasional neurofibroma formation; reduction of EGFR expression in *NF1*<sup>+/-</sup>:p53<sup>+/-</sup> mice decreases tumor formation and mortality  
2005

*NF1* loss in mouse astrocytes preferentially activates K-Ras; astrocyte K-Ras activation mimics effects of *NF1* loss in vitro and in vivo  
2005

Characterization of the natural history of optic nerve gliomas in *NF1*<sup>+/-</sup> mice lacking *NF1* in astrocytes  
2005

mTOR pathway is activated in *NF1* mutant optic nerve gliomas and mTOR inhibition restores normal growth in *NF1*<sup>+/-</sup> astrocytes  
2005

Epigenetic methylation does not play a broad role in *NF1* inactivation but may be an important factor in some tumors  
2005

TLF and TBP reciprocally regulate *NF1* transcription  
2005

Omega-3 and omega-6 fatty acids differentially modulate MPNST growth  
2005

Ras signaling is dynamically regulated by ubiquitin-mediated proteolysis of neurofibromin  
2003

Brain lipid binding protein regulates Schwann cell-axon interactions in peripheral nerve tumors  
2003

*NF1*<sup>+/-</sup> mouse Schwann cells secrete Kit ligand, which stimulates migration of *NF1*<sup>+/-</sup> mast cells  
2003

*NF1*-deficient mast cells have reduced surface Fas antigen expression in response to Kit ligand and are resistant to Fas-ligand mediated apoptosis  
2004

Neurofibromin contains a nuclear localization signal  
2004

Mouse model of plexiform neurofibromas developed  
2002

Cognitive ability does not improve as children with *NF1* develop into adulthood, despite decreases in MRI abnormalities  
2003

Attention deficit hyperactivity disorder is the major risk factor for poor social functioning in children with *NF1*  
2004

*NF1* blood gene expression profiles characterized – potential diagnostic and prognostic markers  
2005

Development and clinical application of five pre-implantation genetic diagnosis protocols for *NF1*  
2005

No correlation found between the type and location of *NF1* gene mutations and the type, location, and size of plexiform neurofibromas  
2002

Analysis of statistical associations among *NF1* clinical features – nine features grouped into three distinct sets  
2003

*NF1* microdeletions associated with increased risk of developing MPNSTs  
2003

No correlation found between the development of café-au-lait spots and neurofibromas in individual body segments of *NF1* patients, but the number of body segments affected is influenced by genetic factors  
2004

Deletion of the *NF1* gene responsible for disease phenotype in at least 4.4% of a cohort of 500 unrelated unselected *NF1* patients  
2004

Optic pathway gliomas may present in older children with *NF1* and progress years after diagnosis  
2004

Subcutaneous neurofibromas associated with increased mortality in adults with *NF1*; facial plexiform neurofibromas and itching associated with elevated mortality in children with *NF1*  
2005

Oral contraceptives do not stimulate neurofibroma growth in women with *NF1*  
2005

Children with *NF1* and low-grade visual pathway gliomas respond well to vincristine and carboplatin and do not develop progressive disease  
2002

Open label Phase I trial of thalidomide in *NF1* patients with plexiform neurofibromas – drug was well tolerated and minor responses were observed in four patients  
2003

FK228, an anti-PAK1 drug, causes complete regression of MPNST xenografts  
2005

NINDS Workshop: Developing Therapies for the Neurofibromatoses  
2003